The First Highly Enantioselective Alkynylation of Chloral: A Practical and Efficient Pathway to Chiral Trichloromethyl Propargyl Alcohols

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Abstract: A new, inexpensive chiral amino alcohol-based ligand, (1*S*,2*S*)-2-*N*,*N*-dimethylamino-1-(4-nitrophenyl)-3-(*tert*-butyloxy)propan-1-ol, was developed for the asymmetric alkynylation of chloral in high yield with up to 98% ee. The resulting chiral adduct (*S*)-1-trichloromethyl-3-phenyl-2-propyn-1-ol was hydrogenated over 10% Pd/C to give the useful intermediate chiral trichloromethyl carbinol in quantitative yield, which was efficiently transformed into the pharmaceutically important building blocks 2-hydroxy-4-phenylbutanoate and homophenylalanine in high yield with excellent enantiomeric excess.

Keywords: 1,2-amino alcohols; chloral; enantioselective alkynylation; N,O ligands; propargyl alcohols; zinc

Introduction

Optically active trichloromethyl carbinols serve as versatile building blocks for asymmetric synthesis. They are not only synthetic equivalents of α-amino acids,[1] but also useful synthons of other chiral compounds, such as α-hydroxy acids,[2] oxiranes[3] and α-fluoro acids.[4] To the best of our knowledge, there was only one general route to chiral trichloromethyl carbinols through the CBS reduction of trichloromethyl ketones.[1] The shortest and atom economic way for the preparation of such a compound would be the direct coupling of chloral with a terminal alkyne. Recently, great progress has been made in the enantioselective nucleophilic alkynylation of aldehydes to give chiral secondary propargylic alcohols using chiral amino alcohols as ligands in the presence of $Zn(OTf)_2$ and Et_3N.[5] Herein we report a practical and efficient process to chiral trichloromethyl carbinols. The process combines highly enantioselective alkynylation of chloral using a new cost-effective chiral amino alcohol ligand, (1*S*,2*S*)-2-*N*,*N*-dimethylamino-1-(4-nitrophenyl)-3-(*tert*-butyloxy)-propan-1-ol.

Results and Discussion

In preliminary studies on the optimized enantioselective conditions, the asymmetric alkynylation of chloral with phenylacetylene was performed (Scheme 1 and Table 1). At first, the reaction was performed with the well known and efficient *N*-methylephedrine ligand combined with $Zn(OTf)_2$ developed by Carreira.[5] However, this ligand proved to be only moderately selective in this alkynylation reaction even when 1.2 equivalents of ligand were used (entry 1). Recently, a new inexpensive chiral amino alcohol ligand based on the simple and short modification of (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)propane-1,3-diol, which is obtained from the commercial chloramphenicol synthesis, was developed in the alkynylation reaction by our group.[6] In subsequent investigations, a series of its derivatives (**1b–g**) were synthesized and evaluated as ligands in an effort to obtain a more efficient enantioselective alkynylation. During the course of screening of the ligands, it was seen that the groups on C2-nitrogen and C3-oxygen of chloramphenicol base greatly affected the enantioselectivity of the reaction (entries 2–7). The best result was obtained by using (1*S*,2*S*)-2-*N*,*N*-dimethylamino-1-(4-nitrophenyl)-3-(*tert*-butyloxy)propan-1-ol (**1d**) as ligand, in which the amino group was substituted with two methyl groups and the C3-position oxygen bears a *t*-butyl group (entry 4). Thus, when the phenylacetylene and chloral were treated with 0.55 equiv. of ligand **1d**, 0.50 equiv. of $Zn(OTf)_2$, and 0.75 equiv. of Et_3N in toluene at room temperature, the trichloromethyl propargyl alcohol adduct was isolated in 83% yield and 97% ee yield after 6 h. Attempts to reduce the amount of catalyst and ligand caused decreases of the enantioselectivity (entry 8).

The enantioselective alkynylations of chloral with various aliphatic and aromatic acetylenes using (1*S*,2*S*)-**1d**

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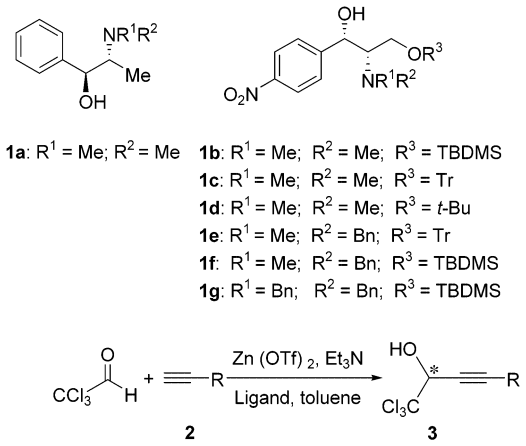
Table 1. Alkynylation of chloral with terminal acetylenes.[a]

Entry	R in alkynes **2**	$Zn(OTf)_2$ (equivs.)	Ligand (equivs.)	Product **3**	Yield [%][b]	ee [%]
1	Ph	1.1	**1a** (1.2)	**3a**	12	62[c]
2	Ph	0.5	**1b** (0.55)	**3a**	31	92[c]
3	Ph	0.5	**1c** (0.55)	**3a**	50	89[c]
4	Ph	0.5	**1d** (0.55)	**3a**	83	97[c]
5	Ph	0.5	**1e** (0.55)	**3a**	28	26[c]
6	Ph	0.5	**1f** (0.55)	**3a**	42	45[c]
7	Ph	0.5	**1 g** (0.55)	**3a**	52	7[c]
8	Ph	0.19	**1d** (0.2)	**3a**	72	84[c]
9	Ph	0.5	**1d** (0.55)	**3a**	93	96[d]
10	Ph	0.5	**1d** (0.55)	**3a**	93	91[e]
11	Ph	0.5	**1d** (0.55)	**3a**	96	94[f]
12	2-phenylethyl	0.5	**1d** (0.55)	**3b**	76	98[g]
13	cyclopropyl	0.5	**1d** (0.55)	**3c**	90	96[h]
14	*t*-butyl	0.5	**1d** (0.55)	**3d**	60	93[h]
15	*n*-butyl	0.5	**1d** (0.55)	**3e**	79	98[h]
16	trimethylsilyl	0.5	**1d** (0.55)	**3f**	70	92[h]
17	$CH_2OTBDMS$	0.5	**1d** (0.55)	**3 g**	71	98[h]
18	cyclopentylmethyl	0.5	**1d** (0.55)	**3 h**	95	95[h]

[a] All reactions carried out at 20 °C in toluene (1 mmol chloral/mL) using Et_3N ($Et_3N:Zn^{2+} = 1.5:1$ equivs.) as base.
[b] Isolated yield.
[c] Determined by chiral HPLC on a Chiralcel OJ column.
[d] 10 mmol scale.
[e] 20 mmol scale reaction and $Zn(OSO_2CF_2H)_2$ was used.
[f] The ligand was recycled 3 times.
[g] Determined by chiral HPLC on a Chiralcel AD column.
[h] Determined by chiral GC on a Chiralcel Rt-βDEXcst™ (Restek) column.

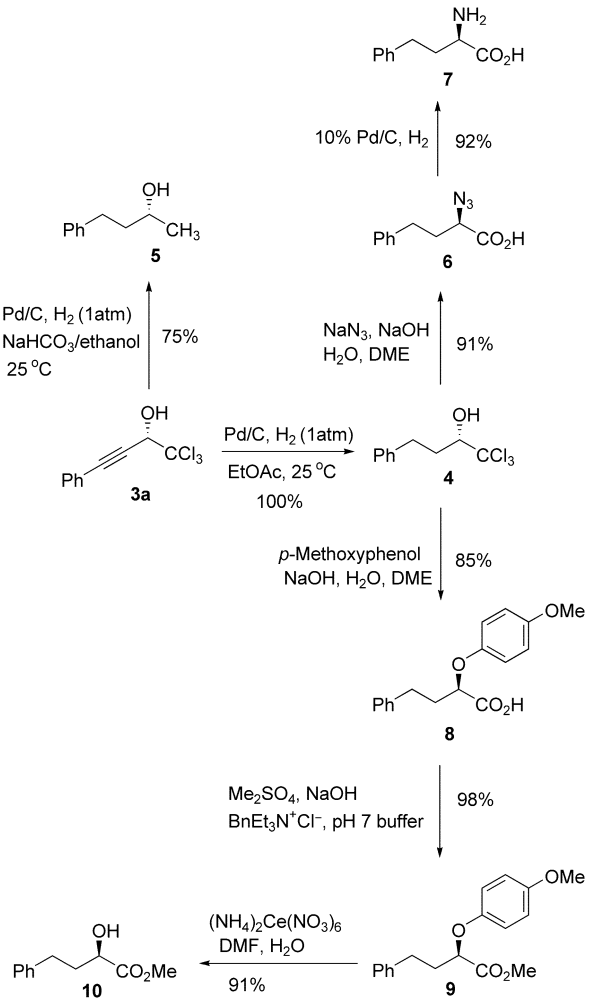


Scheme 1. Alkynylation of chloral with terminal acetylenes.

as ligand are summarized in Table 1 (entries 12–18). All of the propargyl alcohols were obtained with excellent ees (up to 98%) and in high chemical yields, even the bulky *t*-butylacetylene and trimethylsilylacetylene (entries 14 and 16). A 10-mmol scale reaction of phenylacetylene was performed to give the adduct in 93% yield and 96% ee (entry 9). The chiral ligand can be recovered unchanged (96% recovery) and recycled without any decrease of the enantioselectivity (entry 11). The $Zn(ODf)_2$ developed in our group also showed very high activation in this asymmetric alkynylation reaction (entry 10).[7]

Optically active 2-hydroxy-4-phenylbutanoate and homophenylalanine are the key building blocks for the synthesis of biologically active compounds, such as angiotensin-converting enzyme inhibitors, which are effective drugs marketed for the therapy of hypertension and congestive heart failure.[8] For the further studies, transformation of the propargylic trichoromethyl alcohol, the adduct **3a** was selected as a model for the synthesis of chiral hydroxy acid and amino acid, which would open an efficient way to access the compounds. Subsequently investigations showed that this can be realized through simple and short transformations (Scheme 2). Initially, the hydrogenation of compound **3a** was carried out over 10% Pd/C in ethanol in the presence of $NaHCO_3$ at room temperature. Not only the triple bond in **3a** was hydrogenated, but also the trichloromethyl group was reduced to a methyl group to give 4-phenyl-2-butanol (**5**) in 75% yield. However, when the hydrogenation reaction was carried out in EtOAc under 1 atm pressure at room temperature for 4 h, the triple bond was selectively hydrogenated to give the trichloromethyl carbinol **4** in quantitative yield. With the trichoromethyl carbinol **4** in hand, the procedure reported by Corey[1,2] was used for its further conversion into the key building blocks 2-hydroxy-4-phenylbutanoate (**10**) and homophenylalanine (**7**). Treatment of the trichloromethyl carbinol **4**

with NaOH (4 equivs.) and NaN_3 (2 equivs.) in homogeneous solution in aqueous 1,2-dimethoxyethane at room temperature overnight effected conversion to (*R*)-α-azido acid **6**. The reduction of the α-azido acid to homophenylalanine (**7**; 90% yield and 98% ee) was performed with 10% Pd/C in EtOAc under H_2 at 1 atm. The reaction of trichloromethyl carbinols with *p*-methoxyphenol in basic aqueous dimethoxyethane at room temperature gave the corresponding α-*p*-anisyloxy acids **8**. Methylation of the α-*p*-anisyloxy acids followed by the deprotection of PMB with CAN afford the corresponding 2-hydroxy-4-phenylbutanoate **10** (91% yield and 99% ee).



Scheme 2. Conversion of propargylic trichoromethyl alcohol **3a** to the chiral amino acid **7** and hydroxy acid ester **10**.

Conclusion

In conclusion, an efficient and highly enantioselective alkynylation of chloral with terminal acetylenes using a new amino alcohol ligand is reported. This process affords trichloromethylpropargyl alcohol adducts in good to high yields with very high enantionselectivity under mild conditions. The chloral alkynylation adduct with phenylacetylene can be easily converted into a series of important building blocks through simple and short transformations. The process developed here is attractive for the pharmaceutical industry.

Experimental Section

General Remarks

Melting points were measured on a WRS-1A digital melting point apparatus and are uncorrected. Optical rotations were recorded on Perkin-Elmer 341MC instrument. Infrared (IR) spectra were determined with a Shimadzu IR-440 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX-300 or INOVA-600 instrument. The chemical shifts (δ) are expressed in ppm and coupling constants (*J*) are given in Hz. Low-resolution mass spectra were obtained on a VG-Quattro or HP-5969A spectrometer and high-resolution mass spectra were recorded on a Finnigan MAT-95 spectrometer. Microanalyses were carried out with a Heraeus Rapid-CHNO instrument. All moisture-sensitive reactions were done under an argon atmosphere in oven-dried (150 °C) glassware. Flash chromatography was performed using silica gel H (10–40 μm). Standard reagents and solvents were purified according to known procedures

(1*S*,2*S*)-3-(*t*-Butyldimethylsilyloxy)-2-*N*,*N*-dimethylamino-1-(*p*-nitrophenyl)propan-1-ol (1b)

TBDMSCl (3.3 g, 22 mmol) in 50 mL CH_2Cl_2 was added to a solution of (1*S*,2*S*)-2-*N*,*N*-dimethylamino-3-(*p*-nitrophenyl)-propane-1,3-diol (4.8 g, 20 mmol) and Et_3N (3.1 mL, 22 mmol) in CH_2Cl_2 (50 mL) and the mixture was allowed to stand overnight at room temperature. The mixture was washed with water (50 mL) and dried with Na_2SO_4. After removal of the solvent, the crude residue was purified by flash chromatography on silica gel (hexane/EtOAc = 15:1) to afford **1b**; yield: 6.3 g (89%); $[\alpha]_D^{20}$: −15.4 (*c* 1.09, $CHCl_3$); FTIR (KBr): ν = 3344, 2954, 1606, 1525,1349 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.25–8.20 (d, *J* = 8.5 Hz, 2H), 7.6–7.55 (d, *J* = 8.5 Hz, 2H), 4.65 (d, *J* = 9.7 Hz, 1H), 3.77–3.6(dd, *J* = 11.3 Hz, 2.7 Hz 1H), 3.5–3.45(dd, *J* = 11.3 Hz, 6.0 Hz 1H), 2.50 (m, 7H), 1.85 (s, 9H), 0.1 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.2, 147.4, 128.0, 123.3, 69.0, 57.1, 41.6, 25.7, 17.9, −5.9; MS (EI): *m/e* (rel. int.) = 297(M^+ − 57, 0.3), 209 (8.2), 202 (100); anal. calcd. for $C_{17}H_{30}N_2O_4Si$: C 57.60, H 8.53, N 7.90; found: C 57.82, H, 8.18, N 7.77.

(*1S*,*2S*)-1-(*p*-Nitrophenyl)-2-(*N*,*N*-dimethylamino)-3-trityloxypropan-1-ol (1c)

To a solution of (*1S*,*2S*)-2-*N*,*N*-dimethylamino-3-(*p*-nitrophenyl)propane-1,3-diol (1.95 g, 8 mmol) in CH_2Cl_2 (50 mL) were added triphenylmethane chloride (3.34 g, 12 mmol) and Et_3N (2 mL) at 0 °C. The mixture was stirred overnight at room temperature and washed with water (20 mL). The organic layer was dried with Na_2SO_4 and concentrated under vac-

uum. The residue was recrystallized from cyclohexane/ethyl acetate to give **1c**; yield: 3.7 g (95%); $[\alpha]_D^{20}$: −20.4 (*c* 0.50, $CHCl_3$); FTIR (KBr): ν = 3315, 2870, 1601, 1525, 1349 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.09–8.06 (d, *J* = 8.4 Hz, 2H), 7.36–7.33 (d, *J* = 8.6 Hz, 2H), 7.25–7.17 (m, 15H), 4.28–4.25(d, *J* = 10.0 Hz, 1H), 3.28 (dd, *J* = 10.2 Hz, 6.4 Hz 1H), 3.01(dd, *J* = 10.7 Hz, 3.9 Hz, 1H), 2.71 (m, 1H), 2.45 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.1, 147.6, 143.6, 128.9, 128.8, 128.7, 128.6, 128.4, 128.1, 127.9, 127.8, 127.3, 123.7, 87.7, 70.9, 70.6, 58.6, 41.6; MS (EI): *m/e* (rel. int) = 479(M^+ − 3, 0.03), 330 (29), 243 (100).

(*1S,2S*)-1-(*p*-Nitrophenyl)-2-(*N,N*-dimethylamino)-3-(*t*-butyloxy)-propan-1-ol (1d)

Concentrated H_2SO_4 (0.8 g) was added dropwise to a solution of (*1S,2S*)-2-*N,N*-dimethylamino-3-(*p*-nitrophenyl)propane-1,3-diol (1.8 g, 7.5 mmol) in CH_2Cl_2 (20 mL) at 0 °C. Isobutene gas was bubbled for 1 h with the temperature maintained at 0–5 °C. An additional amount of concentrated H_2SO_4 (0.2 g) was added. The mixture was allowed to warm to room temperature and was stirred vigorously for 7 h under isobutene bubbling. Then the mixture was cooled to 0 °C and neutralized with saturated aqueous K_2CO_3 to pH = 7. The separated organic layer was dried with Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (hexane:EtOAc = 10:1) to afford **1d**; yield: 1.44 g (65%); mp 100.0–101.3 °C; $[\alpha]_D^{20}$: −23.5 (*c* 1.0, $CHCl_3$); FTIR (KBr): ν = 3333, 2972, 1606, 1523, 1357, 1197 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 4.59 (d, *J* = 9.9 Hz, 1H), 3.34 (dd, *J* = 3.0 Hz, and 9.9 Hz, 1H), 3.21 (dd, *J* = 6.5 Hz, and 10 Hz, 1H), 2.56 (m, 1H), 2.47 (s, 6H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.6, 147.6, 128.46, 123.49, 73.3, 70.3, 69.8, 56.0, 41.8, 27.4; MS (EI): *m/e*(rel. int.) = 223(M^+ − 73, 3), 209 (21), 144 (68), 88 (100), 71(10), 57(31); anal. calcd. for $C_{15}H_{24}N_2O_4$: C 60.81, H, 8.11, N, 9.46; found: C 60.72, H 8.26, N 9.14.

(1*S*,2*S*)-1-(*p*-Nitrophenyl)-2-(*N*-benzyl-*N*-methylamino)-3-trityloxypropan-1-ol (1e)

A mixture of (*1S,2S*)-2-amino-3-(*p*-nitrophenyl)propane-1,3-diol (2.12 g, 10 mmol), benzaldehyde (1.2 g, 10.5 mmol) and $CuSO_4$ (0.2 g) in methanol (10 mL) was refluxed for 7 h. The mixture was cooled to room temperature, and the solid was filtered. To the filtrate was added THF (10 mL) and $NaBH_4$ (0.4 g). The resulting mixture was refluxed for 2 h and poured into 5% HCl (20 mL). The mixture was extracted with ether (20 mL × 3). The combined extracts were washed with brine and concentrated. The residue as taken up in HCOOH (10 mL) and refluxed with 37% aqueous HCHO (10 mL) for 8 h. After cooling to 0 °C, the mixture was basified to pH = 11–12 with 20% NaOH and extracted with CH_2Cl_2 (15 mL × 3). The combined organic layer was dried with Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (hexane/EtOAc = 1:1) to afford the product; yield: 1.2 g (38% for two steps); FTIR (KBr): ν = 3543, 3208, 2943, 1516, 1350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 10.7 Hz, 2H), 7.50 (d, *J* = 11.0 Hz, 2H), 7.40–7.26 (m, 5H), 4.63 (d, *J* = 9.6 Hz, 1H), 4.01 (d, *J* = 13.1 Hz, 1H), 3.82(d, *J* = 12.7 Hz, 1H), 3.63 (m, 2H), 2.78 (m, 1H) 2.43 (s, 3H); MS (EI): *m/e* (rel. int.) = 317 (M + 1, 0.8), 164 (51), 91 (100).

The above product (380 mg, 1.2 mmol) in CH_2Cl_2 (15 mL) was treated with triphenylmethane chloride (334 mg, 1.2 mmol) and Et_3N (0.2 mL) at 0 °C overnight at room temperature. The mixture was washed with water (10 mL). The separated organic layer was dried with Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (hexane/EtOAc = 15:1) to afford **1e**; yield: 500 mg (75%); mp 58.0–59.3 °C; $[\alpha]_D^{20}$: +47 (*c*, 0.25, $CHCl_3$); FTIR (KBr): ν = 3314, 2926, 1602, 1521,1346 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 8.8 Hz, 2H), 7.40–7.19 (m, 22H), 4.30 (d, *J* = 9.6 Hz, 1H), 3.94 (d, *J* = 13.0 Hz, 1H), 3.73(d, *J* = 6.8 Hz, 1H), 3.36 (m, 1H), 3.06 (m, 1H) 2.89 (m, 1H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.6, 147.6, 143.46, 138.2, 129.3, 128.8, 128.7, 128.6 ,128.4, 128.0, 127.7 127.4, 123.7, 87.8, 70.5, 69.8, 60.1, 58.0, 37.0; MS (EI): *m/e* (rel. int.) = 406 (M^+ − 152, 24.9), 243 (100); anal. calcd. for $C_{15}H_{24}N_2O_4$: C 77.42, H 6.09, N 5.02; found: C 77.26, H 6.06, N, 4.65.

(1*S*,2*S*)-1-(*p*-Nitrophenyl)-2-(*N* -benzyl-*N*-methylamino)-3-(*t*-butyldimethylsilyloxy)propan-1-ol (1f)

TBDMSCl (300 mg, 2 mmol) and imidazole (136 mg, 2 mmol) were added to a solution of (*1S,2S*)-2-(*N*-benzyl-*N*-methylamino)-3-(*p*-nitrophenyl)propane-1,3-diol (632 mg, 2 mmol) in CH_2Cl_2 (15 mL) and the mixture allowed to stand overnight at room temperature. The mixture was washed with water (10 mL). The organic layer was dried with Na_2SO_4 and concentrated under vacuum,. The crude product was purified by flash chromatography on silica gel (hexane/EtOAc = 10:1) to afford **1f**; yield: 570 mg (66%); $[\alpha]_D^{20}$: +42.8 (*c* 0.9, $CHCl_3$); FTIR (KBr): ν = 3344, 2926, 1606, 1525,1348 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 8.9 Hz, 2H), 7.51 (d, *J* = 8.6 Hz), 7.38–7.31 (m, 5H), 4.69 (d, *J* = 9.6 Hz, 1H), 4.02 (d, *J* = 13.0 Hz, 1H), 3.74(d, *J* = 13.3 Hz, 1H), 3.68 (dd, *J* = 11.3 and 6.0 Hz, 1H), 3.58 (dd, *J* = 11.5 and 6.6 Hz, 1H), 2.69 (m, 1H), 2.43 (s, 3H), 0.91 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.5, 147.7, 138.9, 129.2, 128.8, 128.3, 127.7, 123.6, 70.1, 69.3, 60.1, 58.1, 37.6, 26.1, 18.3, −5.5; MS (EI): *m/e* (rel. int.) = 415 (M^+ − 15, 0.9), 278 (100), 91 (72.7).

(1*S*,2*S*)-1-(*p*-Nitrophenyl)-2-(*N,N*-dibenzylamino)-3-(*t*-butyldimethylsilyloxy)propan-1-ol (1g)

K_2CO_3 (10.2 g, 74 mmol) and benzyl bromide (3 mL, 24 mmol) were added to a solution of (1*S*,2*S*)-2-amino-1-(*p*-nitrophenyl)propane-1,3-diol (3.0 g, 14 mmol) in 60 mL DMF at 0 °C. Then the mixture was allowed warm to room temperature. After 50 h, the mixture was poured into the ice/water, extracted with EtOAc (50 mL × 3), dried with Na_2SO_4 and concentrated under vacuum. The crude residue was purified by flash chromatography on silica gel (hexane/EtOAc = 2:1) to afford (1*S*,2*S*)-2-*N,N*-dibenzylamino-1-(*p*-nitrophenyl)propane-1,3-diol; yield: 4.7 g (86%); mp 156.1–158.6 °C; FTIR (KBr): ν = 3442, 1523,1348 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.7 Hz, 2H), 7.42–7.28 (m, 12H), 4.72 (d, *J* = 9.5 Hz,

1H), 4.12 (d, $J=13.3$ Hz, 2H), 3.78–3.69 (m, 4H), 2.85 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.4, 147.6, 138.8, 129.6, 128.9, 128.1, 127.8, 123.8, 70.0, 65.1, 58.7, 54.8; MS (EI): *m/e* (rel. int.) = 361($M^+ - 31$, 0.5), 240 (48.6), 91 (100); anal. calcd. for $C_{23}H_{24}N_2O_4$: C 70.41, H 6.12, N 7.14; found: C 70.38, H 6.23, N 7.16.

The above product (1.96 g, 5 mmol) in CH_2Cl_2 (50 mL) was treated with imidazole (0.816 g, 12 mmol) and TBDMSCl (0.825 g, 5.5 mmol) at 0 °C. The mixture was stirred overnight at room temperature and washed with water (60 mL) and brine. The organic layer was dried with Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (hexane/EtOAc = 6:1) to afford **1g**; yield: 2.3 g (91%); $[\alpha]_D^{20}$: +140.1 (*c* 0.85, $CHCl_3$); FTIR (KBr): ν = 3403, 2931, 1525, 1344 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (d, $J=8.7$ Hz, 2H), 7.40–7.26 (m, 12H), 5.06 (s, 1H), 4.76 (d, $J=9.9$ Hz, 1H), 4.13 (d, $J=13.3$ Hz, 2H), 3.76(dd, $J=11.4$ and 2.3 Hz, 1H), 3.64 (d, $J=12.8$ Hz, 2H), 3.55 (dd, $J=11.4$ and 5.7 Hz, 1H), 2.74 (m, 1H), 0.92 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.5, 147.6, 138.9, 129.5, 128.9, 128.2, 127.8, 123.6, 69.1, 65.2, 58.3, 54.9, 26.1, 18.3, −5.4; MS (ESI): *m/e* (rel. int.) = 507 ($M^+ + 1$); anal. calcd. for $C_{29}H_{38}N_2O_4Si$: C 68.77, H 7.51, N 5.53; found: C 68.63, H 7.35, N 5.41.

General Procedure for the Asymmetric Alkynylation of Choral

To a solution of $Zn(OTf)_2$ (181 mg, 0.50 mmol) and chiral ligand (0.55 mmol), triethylamine (104 μL, 0.75 mmol) in dried toluene (1 mL) was added the terminal acetylene **2** (1.1 mmol) under an argon atmosphere over 2 h at 25 °C. Then chloral (98 μL, 1 mmol) was introduced by a syringe. The mixture was stirred overnight at room temperature and poured into saturated NH_4Cl (10 mL). The mixture was extracted with EtOAc (15 mL × 3) and dried with Na_2SO_4. After removal of the solvent, the crude product was purified by flash chromatography on silica gel (hexane: EtOAc = 15:1) to afforded the trichloromethyl propargylic alcohol.

(*S*)-1-Trichloromethyl-3-phenyl-2-propyn-1-ol (3a): 93% yield and 96% ee as determined by HPLC analysis (Chiralcel OJ, *i*-PrOH/hexane = 5/95, 0.7 mL/min, 254 nm): t_r = 26.9 (minor), 33.2 (major); $[\alpha]_D^{20}$: +19.2 (*c* 1.0, EtOAc); FTIR (neat): ν = 3377, 2242, 1491, 1073, 823 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (m, 2H), 7.37 (m, 3H), 5.06 (s, 1H), 3.38 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.2, 129.6, 128.7, 121.4, 101.3, 88.3, 83.2, 76.0; MS (EI) *m/e* 248 (M^+, 1.5), 131(100).

1-Trichloromethyl-5-phenyl-2-pentyn-1-ol (3b): 76% yield and 98% ee as determined by HPLC analysis (Chiralcel AD, *i*-PrOH/hexane = 5/95, 0.7 mL/min, 254 nm): t_r = 21.9 (minor), 24.0 (major); $[\alpha]_D^{20}$: +10.4 (*c* 1.0, EtOAc); FTIR (neat): ν = 3378, 2242, 1497, 1059 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (m, 5H), 4.80 (s, 1H), 3.08 (s, 1H), 2.90 (t, $J=7.5$ Hz, 2H), 2.61 (dt, $J=1.7$ Hz and 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.65, 129.1, 129.0, 127.1, 89.4, 87.1, 76.0, 75.9, 34.9, 21.5; MS (CI): *m/e* (rel. int.) = 277 (M^+, 2), 169 (100); anal. calcd. for $C_{12}H_{11}Cl_3O$: C 52.17, H 3.99; found: C 52.54, H 3.97.

1-Trichloromethyl-3-cyclopropyl-2-propyn-1-ol (3c): 90% yield and 96% ee as determined by GC analysis [Chiralcel Rt-βDEXcst™ (RESTEK), 120 °C (20 min), 1 °C/min to 150 °C (30 min), 8.0 psi N_2]: t_r = 67.7 (major), 70.7 (minor); $[\alpha]_D^{20}$: +8.4° (*c* 1.0, EtOAc); FTIR (neat): ν = 3392, 2246, 1045, 823 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.76 (s, 1H), 3.32 (s, 1H), 1.31 (m, 1H), 0.81 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 102.0, 93.2, 75.9, 70.1, 9.1, 9.0, 0.0; MS (CI): *m/e* (rel. int.) = 233 ($M^+ - NH_4^+$, 100).

1-Trichloromethyl-3-*t*-butyl-2-propyn-1-ol (3d): 60% yield and 93% ee as determined by GC analysis [Chiralcel Rt-βDEXcst™ (RESTEK),120 °C (20 min), 1 °C/min to 150 °C (30 min), 8.0 psi N_2]: t_r = 42.5(major), 45.5 (minor); $[\alpha]_D^{20}$: +1.7 (*c* 1.0, EtOAc); FTIR (neat): ν = 3349, 2974, 2252, 1262, 1055, 824, 804 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.94 (s, 1H), 3.38 (s, 1H), 1.27 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 102.6, 98.1, 76.0, 74.0, 31.1, 28.2; MS (CI): *m/e* (rel. int.) = 229 (M^+, 3), 175 (100).

1-Trichloromethyl-2-heptyn-1-ol (3e): 79% yield and 98% ee as determined by GC analysis [Chiralcel Rt-βDEXcst™ (RESTEK), 120 °C (20 min), 1 °C/min to 150 °C (30 min), 8.0 psi N_2]: t_r = 69.9 (major), 72.3 (minor); $[\alpha]_D^{20}$: +12.7 (*c* 1.0, EtOAc); FTIR (neat): ν = 3390, 2961, 2243, 1059, 825 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.80 (d, $J=7.4$ Hz, 1H), 3.19 (d, $J=7.9$ Hz, 1H), 2.29 (dt, $J=6.9$ Hz and 1.9 Hz, 2H), 1.49 (m, 4H), 0.93 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 102.1, 90.3, 75.9, 75.2, 30.6, 22.4, 18.9, 14.1; MS (CI): *m/e* (rel. int.) = 229 (M^+, 3), 93 (100).

1-Trichloromethyl-3-trimethylsilyl-2-propyn-1-ol (3f): 70% yield and 92% ee as determined by GC analysis [Chiralcel Rt-βDEXcst™ (RESTEK), 100 °C (30 min), 1 °C/min to 180 °C (20 min), 8.0 psi N_2]: t_r = 60.7(major), 61.2 (minor); $[\alpha]_D^{20}$: +12.6 (*c* 1.2, EtOAc); FTIR (KBr): ν = 3272, 2962, 2192, 1253, 1090, 846 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.78 (d, $J=8.8$ Hz, 1H), 3.03 (d, $J=8.6$ Hz, 1H), 0.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 100.9, 98.8, 94.5, 75.6, −0.3; MS (CI): *m/e* (rel. int.) = 244 (M^+, 2), 93 (100).

1-Trichloromethyl-4-*t*-butyldimethylsilyoxy-2-butyn-1-ol (3g): 71% yield and 98% ee as determined by GC analysis [Chiralcel Rt-βDEXcst™ (RESTEK), 150 °C (10 min), 1 °C/min to 180 °C (40 min), 8.3 psi N_2]: t_r = 67.3(major), 68.6 (minor); $[\alpha]_D^{20}$: +10.4 (*c* 1.0, EtOAc); FTIR (neat): ν = 3381, 2957, 2931, 2860, 1258, 1095, 836 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.84 (d, $J=9.2$ Hz, 1H), 4.39 (d, $J=1.5$ Hz, 2H), 3.11 (d, $J=8.9$ Hz, 1H), 0.90 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 100.8, 86.9, 78.8, 75.2, 51.6, 29.7, 25.7, 18.3, 1.0, −5.2; MS (CI): *m/e* (rel. int.) = 223 [$M^+ - 35$(Cl) – 57(*t*-Bu), 3], 93 (100), 75 (77), 57 (48); anal. calcd. for $C_{11}H_{19}Cl_3SiO_2$: C 41.77, H 6.01; found: C 41.95, H, 6.12.

1-Trichloromethyl-4-cyclopentyl-2-butyn-1-ol (3h): 95% yield and 95% ee as determined by GC analysis [Chiralcel Rt-βDEXcst™ (RESTEK), 150 °C (20 min), 1 °C/min to 180 ° (30 min), 10.0 psi N_2]: t_r = 59.4(major), 60.3 (minor); $[\alpha]_D^{20}$: +25.0 (*c* 1.0, EtOAc); FTIR (neat): ν = 3393, 2955, 2869, 2242, 1057, 823 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.78 (dt, $J=2.2$ and 8.6 Hz, 1H), 2.94 (d, $J=9.3$ Hz, 1H), 2.28 (dd, $J=2.2$ and 6.7 Hz, 2H), 2.06(m, 1H), 1.83–1.74(m, 2H), 1.66–1.47(m, 4H), 1.32–1.21(m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 89.5, 75.6, 74.8, 38.8, 32.2, 25.5, 24.6; MS (CI): *m/e* (rel. int.) = 220 [$M^+ - 35$(Cl), 1], 137 (100), 91 (31), 69 (77), 41 (76); anal. calcd. for $C_{10}H_{13}Cl_3O$: C 47.24, H 5.12; found: C 47.36, H 5.15.

(*R*)-4-Phenyl-2-butanol (5)

A solution of 496 mg (2 mmol) (*S*)-1-trichloromethyl-3-phenyl-2-propyn-1-ol in 10 mL EtOH was hydrogenated with 10% Pd/C at 25 °C for 4 h in the presence of $NaHCO_3$ (100 mg). The reaction mixture was filtered and concentrated under vacuum. Purification on silica gel (hexane/EtOAc = 8:1) gave 4-phenyl-2-butanol; yield: 225 mg (75%); $[\alpha]_D^{20}$: +17.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.16 (m, 5H), 3.87–3.80 (m, 1H), 2.82–2.62 (m, 2H), 1.82–1.74 (m, 2H), 1.23 (d, *J* = 6.1 Hz, 3H).

(*S*)-4-Phenyl-1,1,1,-trichloro-2-butanol (4)

A solution of 2.48 g (10 mmol) (*S*)-1-trichloromethyl-3-phenyl-2-propyn-1-ol in 50 mL EtOAc was hydrogenated with 10% Pd/C at 25 °C for 4 h. The reaction mixture was filtered and concentrated under vacuum to give the product; 100% yield and 97.7% ee as determined by HPLC analysis (Chiralcel OJ, *i*-PrOH/hexane = 5/95, 0.7 mL/min, 254 nm): t_r = 11.7 (major), 18.4 (minor); $[\alpha]_D^{20}$: −38.4 (*c* 1.0, $CHCl_3$); FTIR (KBr): ν = 3558, 3453, 3029, 1497, 1455, 1096 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.27 (m, 5H), 4.05 (ddd, *J* = 10.2, 5.4 and 2.0 Hz, 1H), 3.07 (m, 1H), 2.90 (dd, *J* = 5.4 Hz and 1.6 Hz, 1H), 2.83 (m, 1H), 2.45 (m, 1H), 2.05 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.0, 128.9, 128.8, 126.6, 104.4, 82.2, 33.2, 32.2; MS (EI): *m/e* (rel. int.) = 252 (M^+, 5), 216 (4), 117 (21), 91 (100).

(*R*)-Homophenylalanine (7)

The compound **7** was prepared in 92% yield by the procedure of Corey;[1] $[\alpha]_D^{20}$: −47.1 (*c* 1.0, 1N HCl); FTIR (KBr): ν = 3400–2900, 1584, 1140 cm^{-1}; ^{1}H NMR (300 MHz, D_2O, TFA): δ = 6.91–6.80 (m, 5H), 3.59 (t, *J* = 6.0 Hz, 1H), 2.34–2.27 (m, 2H), 1.83–1.70 (m, 2H); ^{13}C NMR (75 MHz, D_2O, TFA): δ = 171.6, 139.8, 128.6, 128.3, 126.5, 52.1, 31.3, 30.1; MS (EI): *m/e* (rel. int.) =179 (M^+, 3), 162 (17), 134 (37), 91 (100).

(*R*)-Methyl-2-hydroxy-4-phenylbutanoate (10)

The compound **10** was prepared in 91% yield by the procedure of Corey;[2] $[\alpha]_D^{20}$: −28.1 (*c*, 2.0, $CHCl_3$); FTIR (neat): ν = 3476, 1736, 1101 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.17 (m, 5H), 4.19 (dd, *J* = 8.0 and 4.2 Hz, 1H), 3.75 (s, 3H), 2.83–2.74 (m, 3H), 2.10 (m, 1H), 1.96 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.6, 141.0, 128.5, 128.4, 126.0, 69.6, 52.5, 35.8, 30.9; MS (EI): *m/e* (rel. int.) = 194 (M^+, 7), 117 (15), 91 (100).

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